American Journal of Epidemiology

Vol. 160, No. 8
Printed in U.S.A.
DOI: 10.1093/aje/kwh278

Menstrual and Reproductive Factors and Risk of Non-Hodgkin's Lymphoma among Connecticut Women

Yawei Zhang[1], Theodore R. Holford[1], Brian Leaderer[1], Peter Boyle[2], Shelia Hoar Zahm[3], Bing Zhang[4], Kaiyong Zou[5], Lindsay M. Morton[1], Patricia H. Owens[1], Stuart Flynn[6], Giovanni Tallini[6], and Tongzhang Zheng[1]

[1] Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, CT.
[2] Department of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy.
[3] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.
[4] Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada.
[5] Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, CT.
[6] Department of Pathology, Yale University School of Medicine, New Haven, CT.

Received for publication December 3, 2003; accepted for publication May 11, 2004.

Several recent studies have suggested a potential role of menstrual and reproductive factors in the risk of non-Hodgkin's lymphoma. To further examine the relation, the authors analyzed data from a population-based case-control study of non-Hodgkin's lymphoma in Connecticut women between 1996 and 2000. A total of 601 histologically confirmed cases and 717 randomly selected population-based controls were included in this study. An in-person interview was conducted using a standardized and structured questionnaire to collect information on menstrual and reproductive factors and potential confounding factors. Compared with nulliparous women, women who had four or more pregnancies during their lifetime were found to have a significantly reduced risk of non-Hodgkin's lymphoma (odds ratio (OR) = 0.6, 95% confidence interval (CI): 0.4, 0.9). Risk appeared to decrease with increasing number of pregnancies (p_{trend} = 0.03). The authors also observed an increased risk of non-Hodgkin's lymphoma overall (OR = 1.5, 95% CI: 1.0, 2.2) and of diffuse non-Hodgkin's lymphoma (OR = 1.7, 95% CI: 1.1, 2.7) for women who started their first menstrual period at age 15 or more years compared with those who started their first menstrual period before age 12 years. These findings support a reduced risk of non-Hodgkin's lymphoma associated with multiple pregnancies and an increased risk of non-Hodgkin's lymphoma associated with later age at menarche.

case-control studies; Connecticut; lymphoma, non-Hodgkin; menstruation; reproduction; risk factors; women

Abbreviations: CI, confidence interval; OR, odds ratio.

The incidence of non-Hodgkin's lymphoma has been increasing worldwide (1–3). Little is known, however, about the etiology of non-Hodgkin's lymphoma and the factors responsible for the observed increase. Several epidemiologic studies have suggested a relation of menstrual and reproductive factors to the risk of non-Hodgkin's lymphoma (4–11). A relation between reproductive factors and non-Hodgkin's lymphoma risk is biologically plausible, since estrogen levels increase dramatically during pregnancy (12), and exposure to high levels of estrogen is associated with a reduced secretion of interleukin-6, which is a growth factor for intermediate- and high-grade non-Hodgkin's lymphoma (13–19).

Epidemiologic studies linking reproductive factors to non-Hodgkin's lymphoma risk, however, have been inconsistent. One study from Sweden reported a reduced risk of non-Hodgkin's lymphoma associated with parity (5), while another study from Italy reported an increased risk (4). Three other studies (7–9) also reported a slightly increased risk of non-Hodgkin's lymphoma associated with parity. Later age at first full-term pregnancy was related to an increased risk of non-Hodgkin's lymphoma in one study (6) but not in another (10). A study from Italy by La Vecchia et al. (10)

Correspondence to Dr. Tongzhang Zheng, 129 Church Street, Suite 700, New Haven, CT 06510 (e-mail: tongzhang.zheng@yale.edu).

also found no association among number of births, number of abortions, and risk of lymphomas.

So far, few studies have investigated the risk of non-Hodgkin's lymphoma associated with menstrual and reproductive factors by non-Hodgkin's lymphoma subtypes. This is important, however, because non-Hodgkin's lymphoma represents a heterogeneous group of lymphoma disorders (20). Further study of menstrual and reproductive factors and non-Hodgkin's lymphoma risk by subtype of non-Hodgkin's lymphoma is clearly warranted. Here, we report the findings linking menstrual and reproductive factors to non-Hodgkin's lymphoma risk using the data from a population-based case-control study of non-Hodgkin's lymphoma among Connecticut women.

MATERIALS AND METHODS

Study population

A detailed description of the study population has been published elsewhere (21). In brief, cases included histologically confirmed (*International Classification of Diseases for Oncology,* Second Edition (22), codes M-9590–9595, 9670–9688, 9690–9698, 9700–9723) incident non-Hodgkin's lymphoma patients, aged 21–84 years, who had no previous diagnosis of cancer with the exception of nonmelanoma skin cancer. All subjects were diagnosed in Connecticut between 1996 and 2000 and were alive at the time of interview. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource, an agent of the Connecticut Tumor Registry. Of 832 eligible cases, 601 (72 percent) completed in-person interviews.

To provide accurate and consistent histologic classification of the cases, pathology slides (or tissue blocks) were obtained for all cases from the pathology departments where the cases were diagnosed. Each specimen was reviewed by two experienced study pathologists (S. F., G. T.). The non-Hodgkin's lymphoma cases were classified according to the Working Formulation and grouped by *grade*: low (M-9670, 9691–9692, 9695–9696), intermediate (M-9591–9593, 9595, 9672, 9675–9676, 9680–9683, 9688, 9693, 9697–9698), and high (M-9684–9687, 9694); by *histologic type*: diffuse (M-9591–9593, 9595, 9670, 9672–9677, 9680–9684, 9686–9688, 9694) and follicular (M-9690–9693, 9695–9698); and by *immunologic type*: B cell (M-9591–9593, 9595, 9670–9674, 9677, 9680–9684, 9686–9688, 9690–9698) and T cell (M-9700–9723).

Population-based controls with Connecticut addresses were recruited using either random digit dialing methods for those below age 65 years or Centers for Medicare and Medicaid Service files for those aged 65 years or above. The participation rate for random digit dialing controls was 69 percent and for Centers for Medicare and Medicaid Service controls was 47 percent. Cases and controls were frequency matched by age in 5-year groups by adjusting the number of controls randomly selected in each age stratum every few months.

Data collection

All procedures were performed in accordance with a protocol approved by the human investigations committees at Yale University, the Connecticut Department of Public Health, and the National Cancer Institute. After approval by each subject's physician (for cases) or following selection through random sampling (for controls), potential participants were approached by letter and/or by phone. Those who consented were interviewed by trained interviewers, either in their homes or at a location convenient for the patient. A standardized, structured questionnaire was used to obtain information on menstrual and reproductive history and other major known or suspected risk factors that might confound the association between menstrual and reproductive history and risk of non-Hodgkin's lymphoma.

Information on menstrual history was collected by asking subjects their age at first menstrual period and whether they still were having menstrual periods, not including those periods due to estrogen replacement therapy. For age at last menstrual period, we asked subjects to report their age at the last natural menstrual period. Information on age at surgical menopause was not collected in this study. Information on reproductive factors was collected by asking subjects whether they had ever had a pregnancy, their age at first livebirth (or stillbirth), and the numbers of pregnancies, livebirths, stillbirths, miscarriages, and abortions. Information on oral contraceptive use was collected, together with other medication uses, by asking participants the question, "Have you ever taken any medicines at least once a day for a period of 6 months or longer previous to 1 year ago?" If yes, subjects were asked to provide information on each medication they had ever taken, the ages at first and last use, and the total months of use.

Data on other potential confounding factors, including family history of cancer, diet, occupation, tobacco use, alcohol consumption, and demographic factors, were also gathered during the interview. Dietary information was collected using a scannable, semiquantitative food frequency questionnaire developed and validated by the Fred Hutchinson Cancer Research Center (23).

Statistical analysis

Age at menarche was defined as the age when subjects had their first menstrual period. Total months of ovulation were calculated according to the method described by Casagrande et al. (24): The age at first menstrual period was subtracted from the age at last natural menstrual period and converted into months by multiplying by 12. The total months of pregnancies (12 months for each livebirth or stillbirth (24, 25)) and the total months of oral contraceptive use were then subtracted to yield the total months of ovulation. As stated by Vorherr (25), the reason for assigning 12 months for each livebirth or stillbirth is that ovulation returns by 6–12 weeks postpartum in general.

Unconditional logistic regression was used to estimate the association between menstrual and reproductive factors and risk of non-Hodgkin's lymphoma by histologic type, immu-

TABLE 1. Selected baseline characteristics of non-Hodgkin's lymphoma cases and controls, Connecticut, 1996–2000

	Cases		Controls	
	No.	%	No.	%
Age (years) ($\chi^2 = 0.78$, $p = 0.68$)				
<50	119	19.8	155	21.6
50–70	277	46.1	317	44.2
>70	205	34.1	245	34.2
Race ($\chi^2 = 2.96$, $p = 0.23$)				
White	571	95.0	667	93.0
Black	18	3.0	25	3.5
Others	12	2.0	25	3.5
Tobacco smoking* ($\chi^2 = 0.00$, $p = 0.99$)				
Never	270	44.9	323	45.0
Ever	331	55.1	394	55.0
Alcohol drinking† ($\chi^2 = 4.78$, $p = 0.03$)				
Never	230	38.2	233	32.5
Ever	371	61.8	484	67.5
Educational level ($\chi^2 = 5.70$, $p = 0.02$)				
High school or less	261	43.4	265	37.0
College or higher	340	56.6	452	63.0
Body mass index ($\chi^2 = 6.24$, $p = 0.04$)				
<25	298	49.6	404	56.4
25–29.99	187	31.1	199	27.7
>29.99	116	19.3	114	15.9
First-degree relative with non-Hodgkin's lymphoma ($\chi^2 = 2.96$, $p = 0.09$)				
No	592	98.5	713	99.4
Yes	9	1.5	4	0.6
Menopausal status ($\chi^2 = 13.45$, $p < 0.01$)				
Premenopausal	88	14.6	162	22.6
Postmenopausal	513	85.4	555	77.4
Non-Hodgkin's lymphoma subtypes				
By histology				
Diffuse	346	57.6		
Follicular	134	22.3		
Other	121	20.1		
By immunologic cell type				
B cell	473	78.7		
T cell	44	7.3		
Other	84	14.0		
By tumor grade				
Low grade	177	29.5		
Intermediate grade	286	47.5		
High grade	18	3.0		
Other	120	20.0		

* Women who reported smoking a total of 100 cigarettes or more during their lifetime were defined as ever smokers. Women who reported smoking less than a total of 100 cigarettes during their lifetime were defined as never smokers.

† Women who reported consumption of 12 drinks or more per year of any type of alcohol during their lifetime were defined as ever drinkers. Women who reported consumption of less than 12 drinks per year of any type of alcohol during their lifetime were defined as never drinkers.

nologic type, and tumor grade and to control for potential confounders. Potential confounding variables included in the final model were age, body mass index (<25, 25–29.99, >29.9 kg/m^2), family history of non-Hodgkin's lymphoma among first-degree relatives, and menopausal status. Adjustments of other variables, such as race, level of education, fruit intake, daily total fat intake, daily animal protein intake, and farming history, did not result in material changes for the observed associations and, thus, were not included in the final model. Use of lifetime pack-years of cigarette smoking (or ever vs. never) and lifetime kilograms of alcohol consumption (or ever vs. never) to control for the potential confounding from smoking and drinking also did not result in material change in the association; thus, tobacco smoking and alcohol consumption were also excluded from the final model. Odds ratios and 95 percent confidence intervals were calculated using SAS statistical software (SAS Institute, Inc., Cary, North Carolina). The multivariate model used original values rather than categorical indexes for continuous variables to test for linear trends. For women who had never been pregnant, we treated their number of pregnancies and age at first pregnancy as missing values when the linear trend was tested.

RESULTS

Table 1 presents the distribution of selected baseline characteristics for the cases and controls. More cases than controls reported a family history of non-Hodgkin's lymphoma, a higher body mass index, and having their last natural menstrual period. Controls reported a higher level of education, and more controls reported ever having consumed alcohol. The distribution of other factors, such as age, race, and tobacco use, was quite similar between the cases and the controls.

As shown in table 2, compared with women who had their first menstrual period before age 12 years, women who had their first menstrual periods at age 15 years or above experienced a 50 percent increased risk of non-Hodgkin's lymphoma. Use of oral contraceptives overall was not associated with the risk of non-Hodgkin's lymphoma. The results by duration of use and by time period of use, however, are suggestive of a reduced risk. Women who used oral contraceptives for more than 5 years had an odds ratio of 0.8 (95 percent confidence interval (CI): 0.5, 1.3) compared with those who used the products for 5 years or less. Women who used oral contraceptives and started before 1970 also showed a reduced risk (odds ratio (OR) = 0.7, 95 percent CI: 0.4, 1.3) compared with those who started using them in 1970 or later. The risk was the lowest for those who used oral contraceptives for more than 5 years and began before 1970 (OR = 0.6, 95 percent CI: 0.3, 1.2). Age at menopause and months of ovulation did not show a clear risk pattern for non-Hodgkin's lymphoma.

As shown in table 3, further analysis by non-Hodgkin's lymphoma subtype for age at first menstrual period showed an increased risk of diffuse non-Hodgkin's lymphoma (OR = 1.7, 95 percent CI: 1.1, 2.7) and B-cell non-Hodgkin's lymphoma (OR = 1.5, 95 percent CI: 1.0, 2.2) for women who had their first menstrual period at age 15 years or above

TABLE 2. Risk of non-Hodgkin's lymphoma associated with menstrual history, Connecticut, 1996–2000

	No. of cases	No. of controls	Odds ratio*	95% confidence interval
Age (years) at menarche†				
<12	119	148	1.0	
12	137	182	1.0	0.7, 1.4
13	163	201	1.1	0.8, 1.5
14	91	105	1.1	0.8, 1.7
≥15	88	80	1.5	1.0, 2.2
Missing	3	2		
p_{trend}			0.07	
Oral contraceptive use†				
Never	472	557	1.0	
Ever	129	160	1.1	0.8, 1.5
Duration of oral contraceptive use (years)†				
≤5	73	80	1.0	
>5	56	80	0.8	0.5, 1.3
p_{trend}			0.49	
Year started using oral contraceptives†				
1970 or after	61	91	1.0	
Before 1970	68	89	0.7	0.4, 1.3
Duration and time period of use of oral contraceptives†				
≤5 years (1970 and after)	39	44	1.0	
≤5 years (before 1970)	34	36	0.7	0.3, 1.4
>5 years (1970 and after)	29	45	0.8	0.4, 1.5
>5 years (before 1970)	27	35	0.6	0.3, 1.2
Age (years) at menopause				
<43	133	139	1.0	
43–48	134	125	1.2	0.9, 1.7
49–52	143	176	0.9	0.7, 1.3
>52	96	107	1.1	0.7, 1.5
Missing	7	8		
p_{trend}			0.88	
Months of ovulation				
<301	129	126	1.0	
301–390	144	147	1.1	0.8, 1.5
391–435	123	140	0.9	0.7, 1.4
>435	108	132	0.9	0.6, 1.3
Missing	9	10		
p_{trend}			0.90	

* Adjusted for age, family history of non-Hodgkin's lymphoma, and body mass index.

† Adjusted for menopausal status.

compared with those who had their first menstrual period before age 12 years.

Table 4 presents the association between reproductive factors and risk of non-Hodgkin's lymphoma. Women who

TABLE 3. Risk of non-Hodgkin's lymphoma subtype associated with age at menarche, Connecticut, 1996–2000

	<12 years			12 years			13 years			14 years			≥15 years		
	No. of cases	No. of controls	Odds ratio*	No. of cases	No. of controls	Odds ratio*	95% confidence interval	No. of cases	No. of controls	Odds ratio*	95% confidence interval	No. of cases	No. of controls	Odds ratio*	95% confidence interval
By histology															
Follicular	30	148	1.0	28	182	0.8	0.4, 1.4	39	200	1.0	0.6, 1.7	21	105	1.0	0.6, 1.9	16	80	1.1	0.5, 2.1
Diffuse	62	148	1.0	82	182	1.1	0.7, 1.6	93	200	1.2	0.8, 1.7	55	105	1.3	0.8, 2.0	53	80	1.7	1.1, 2.7
Other	27	148	1.0	27	182	0.8	0.5, 1.5	31	200	0.9	0.5, 1.5	15	105	0.8	0.4, 1.5	19	80	1.4	0.7, 2.5
By immunologic cell type															
B cell	93	148	1.0	108	182	1.0	0.7, 1.4	134	200	1.1	0.8, 1.6	69	105	1.1	0.7, 1.7	67	80	1.5	1.0, 2.2
T cell	13	148	1.0	8	182	0.6	0.2, 1.4	8	200	0.5	0.2, 1.3	7	105	0.8	0.3, 2.2	8	80	1.3	0.5, 3.3
Other	13	148	1.0	21	182	1.3	0.6, 2.6	21	200	1.2	0.6, 2.4	15	105	1.6	0.7, 3.5	13	80	1.8	0.8, 4.2
By grade															
Low	29	148	1.0	37	182	1.1	0.6, 1.8	56	200	1.5	0.9, 2.4	29	105	1.4	0.8, 2.5	26	80	1.7	0.9, 3.0
Intermediate/high	63	148	1.0	73	182	1.0	0.7, 1.5	77	200	1.0	0.6, 1.4	47	105	1.1	0.7, 1.8	43	80	1.4	0.9, 2.3
Other	27	148	1.0	27	182	0.8	0.5, 1.5	30	200	0.8	0.5, 1.5	15	105	0.8	0.4, 1.6	19	80	1.4	0.7, 2.7

* Adjusted for age, family history of non-Hodgkin's lymphoma, body mass index, and menopausal status.

TABLE 4. Risk of non-Hodgkin's lymphoma associated with reproductive history, Connecticut, 1996–2000

	No. of cases	No. of controls	Odds ratio*	95% confidence interval
History of pregnancy				
Never	71	72	1.0	
Ever	530	645	0.8	0.6, 1.1
1	58	62	0.9	0.6, 1.5
2	151	159	0.9	0.6, 1.4
3	141	166	0.8	0.5, 1.2
≥4	180	258	0.6	0.4, 0.9
p_{trend}			0.03	
No. of livebirths				
Nulliparous	71	72	1.0	
1	78	79	1.0	0.6, 1.6
2	161	174	0.9	0.6, 1.3
3	96	118	0.8	0.5, 1.2
≥4	180	258	0.6	0.4, 0.9
p_{trend}			0.008	
Age (years) at first livebirth				
<20	58	88	1.0	
20–24	178	201	1.3	0.9, 1.9
25–29	172	190	1.4	0.9, 2.1
30–34	45	75	1.0	0.6, 1.7
≥35	24	30	1.4	0.7, 2.6
p_{trend}			0.56	
No. of stillbirths				
0	513	630	1.0	
≥1	17	15	1.5	0.7, 3.0
No. of miscarriages				
0	386	444	1.0	
≥1	144	201	0.8	0.6, 1.1
No. of abortions				
0	492	595	1.0	
≥1	38	50	1.1	0.7, 1.7

* Adjusted for age, family history of non-Hodgkin's lymphoma, body mass index, and menopausal status.

reported ever having had a pregnancy had a slightly reduced risk of non-Hodgkin's lymphoma compared with those who had never had a pregnancy (OR = 0.8, 95 percent CI: 0.6, 1.1). The risk decreased with increasing number of pregnancies (p_{trend} = 0.03). Women who had four or more pregnancies during their lifetime had a significantly reduced risk of non-Hodgkin's lymphoma (OR = 0.6, 95 percent CI: 0.4, 0.9) compared with those who were never pregnant. A similar association was also observed when pregnancy was limited to number of livebirths. A history of abortion, miscarriage, or stillbirth was not significantly associated with non-Hodgkin's lymphoma risk.

TABLE 5. Risk of non-Hodgkin's lymphoma subtype associated with history of pregnancy, Connecticut, 1996–2000

	Nulliparous			Ever parous			One or two pregnancies			Three pregnancies			Four or more pregnancies		
	No. of cases	No. of controls	Odds ratio*	No. of cases	No. of controls	Odds ratio*	95% confidence interval	No. of cases	No. of controls	Odds ratio*	95% confidence interval	No. of cases	No. of controls	Odds ratio*	95% confidence interval
By histology															
Follicular	16	72	1.0	118	645	0.8	0.4, 1.4	53	221	1.1	0.6, 2.0	25	166	0.7	0.3, 1.3	40	258	0.6	0.3, 1.2
Diffuse	41	72	1.0	305	645	0.8	0.5, 1.2	110	221	0.8	0.5, 1.3	92	166	1.0	0.6, 1.5	103	258	0.6	0.4, 1.0
Other	14	72	1.0	107	645	0.8	0.4, 1.5	46	221	1.1	0.5, 2.1	24	166	0.7	0.3, 1.4	37	258	0.7	0.3, 1.3
By immunologic cell type															
B cell	54	72	1.0	419	645	0.8	0.6, 1.2	159	221	0.9	0.6, 1.4	117	166	0.9	0.6, 1.4	143	258	0.7	0.4, 1.0
T cell	7	72	1.0	37	645	0.5	0.2, 1.2	18	221	0.7	0.3, 1.8	7	166	0.4	0.1, 1.1	12	258	0.4	0.2, 1.1
Other	10	72	1.0	74	645	0.8	0.4, 1.7	32	221	1.1	0.5, 2.4	17	166	0.7	0.3, 1.7	25	258	0.7	0.3, 1.5
By grade															
Low	19	72	1.0	158	645	0.9	0.5, 1.5	60	221	1.0	0.6, 1.8	44	166	1.0	0.5, 1.8	54	258	0.7	0.4, 1.3
Intermediate/high	38	72	1.0	266	645	0.7	0.5, 1.1	103	221	0.8	0.5, 1.3	73	166	0.8	0.5, 1.3	90	258	0.6	0.4, 0.9
Other	14	72	1.0	106	645	0.8	0.4, 1.5	46	221	1.1	0.5, 2.1	24	166	0.7	0.3, 1.4	36	258	0.7	0.3, 1.3

* Adjusted for age, family history of non-Hodgkin's lymphoma, body mass index, and menopausal status.

The risk of non-Hodgkin's lymphoma associated with pregnancy by non-Hodgkin's lymphoma subtype is presented in table 5. Compared with nulliparous women, parous women were generally at lower risk of all non-Hodgkin's lymphoma subtypes, although none of the associations was statistically significant. For parous women who had four or more children, a borderline significantly reduced risk was observed for diffuse non-Hodgkin's lymphoma (OR = 0.6, 95 percent CI: 0.4, 1.0) and B-cell non-Hodgkin's lymphoma (OR = 0.7, 95 percent CI: 0.4, 1.0), and a significantly reduced risk was observed for intermediate- and high-grade non-Hodgkin's lymphoma (OR = 0.6, 95 percent CI: 0.4, 0.9).

DISCUSSION

In this population-based case-control study, we found a reduced risk of non-Hodgkin's lymphoma for women who had four or more pregnancies during their lifetime and an increased risk of non-Hodgkin's lymphoma for women who had later age at their first menstrual periods. A reduced risk associated with pregnancies was more pronounced for diffuse, B-cell, and intermediate- and high-grade non-Hodgkin's lymphoma.

The relation between pregnancy or livebirths and non-Hodgkin's lymphoma from previous epidemiologic studies has been inconclusive. In a nested case-control study from Sweden, Adami et al. (5) reported a weak, negative association between parity and risk of non-Hodgkin's lymphoma (p_{trend} = 0.11). A 10–40 percent reduced risk within 5–14 years after the last birth was observed among women with various parities in this study. The Iowa Women's Health Study (7) reported an odds ratio of 0.8 (95 percent CI: 0.6, 1.2) for women who had more than four livebirths compared with those who had only one or two livebirths. In that study, however, nulliparous status was also associated with a nonsignificantly reduced risk (OR = 0.6, 95 percent CI: 0.3, 1.1). A study by Tavani et al. (4) from Italy, however, reported a potentially increased risk of non-Hodgkin's lymphoma associated with pregnancy among women aged less than 50 years. Compared with that for nulligravidas, odds ratios of 2.2 (95 percent CI: 1.1, 4.6) for parous women, 2.4 for women reporting one or two births, and 1.4 for those reporting three or more births were observed in the Italian study. Two other studies involving relatively small numbers of lymphoma cases also suggested a small, nonsignificantly increased risk of lymphatic and hematopoietic cancers (8) or lymphomas (10) associated with parity. Several earlier studies also investigated the relation among miscarriage (7, 9), abortion (4, 7, 9, 11), and non-Hodgkin's lymphoma risk, and none of the studies found an association, which was consistent with our study results.

The biologic mechanisms linking pregnancy or birth to non-Hodgkin's lymphoma risk are currently unclear. Since various primary and acquired immunodeficiencies are established risk factors for non-Hodgkin's lymphoma (26, 27), it is natural to ask whether pregnancy affects non-Hodgkin's lymphoma risk through pregnancy-related changes in immune function. However, as recently reviewed by Luppi (28), pregnancy is associated with a generalized inflammatory response; that is, the innate immune system is activated, while the adaptive immune system is suppressed. The net impact of pregnancy on immune function is a general balance between enhancement and suppression, leaving maternal defenses intact. Thus, in terms of immunodeficiency, pregnancy itself is unlikely to be strongly related to the risk of non-Hodgkin's lymphoma.

On the other hand, pregnancy-related sex hormone changes may have an impact on the observed relation between pregnancy and non-Hodgkin's lymphoma risk. Pregnancy is associated with a dramatic increase in circulating estrogen levels (12). Both experimental and observational studies have shown that estrogens inhibit interleukin-6 secretion (13–17), which has been suggested as a potent growth factor for intermediate- and high-grade non-Hodgkin's lymphoma (18, 19). In our study, pregnancy or livebirth was associated with a reduced risk of non-Hodgkin's lymphoma (table 4), but a significantly reduced risk was seen only for intermediate- and high-grade non-Hodgkin's lymphoma, which was consistent with these studies.

Interestingly, the Iowa Women's Study (7) reported a reduced risk of non-Hodgkin's lymphoma associated with breastfeeding and suggested that a reduced cumulative exposure to estrogen from a delay in the reestablishment of ovulation or a heightened exposure to prolactin could be among the potential reasons for a link between breastfeeding and reduced non-Hodgkin's lymphoma risk. Unfortunately, we are unable to evaluate the relation between breastfeeding and non-Hodgkin's lymphoma risk, because we did not collect this information in our study.

As in our study, most of the earlier studies found no relation between age at first full-term pregnancy (or livebirth) and non-Hodgkin's lymphoma risk (4, 5, 7, 9), except the study by Olsson et al. (6), which reported a sevenfold increased risk associated with women who had their first full-term pregnancy at age 30 years or above compared with those who had their first full-term pregnancy before age 30 years. This study also showed that women with a combination of late age at first full-term pregnancy and low parity are at special risk of developing malignant lymphoma. The interpretation of study results from this study, however, was hampered by the fact that the study included only 79 non-Hodgkin's lymphoma cases.

To the best of our knowledge, only the Iowa Women's Study (7) reported the findings relating age at menarche and non-Hodgkin's lymphoma risk. That study reported a slightly elevated but nonsignificant odds ratio of 1.2 among women who had their first menstrual period at age 15 years or above relative to those who reported having had their first menstrual period when they were below age 12 years (p_{trend} = 0.72). In our study, a borderline-significant, increased odds ratio of 1.5 was observed for women who had their first menstrual period at age 15 years or above compared with those who had their first menstrual period when they were below age 12 years. If exposure to a higher level of estrogens is the underlying reason linking pregnancy to a reduced risk of non-Hodgkin's lymphoma, then later age at menarche would result in a later age at exposure to endogenous hormones at the critical development period, which may

cause an increased risk of non-Hodgkin's lymphoma associated with later age at menarche, as observed in our study.

Oral contraceptive use has been reported to reduce the risk of non-Hodgkin's lymphoma. Schiff et al. (29) reported a reduced risk of primary central nervous system lymphoma among women who had ever used oral contraceptives compared with those who had never used oral contraceptives. A recent population-based case-control study from the Netherlands (30) reported an odds ratio of 0.6 (95 percent CI: 0.2, 2.3) for those with the longest duration of oral contraceptive use. Nelson et al. (9) found that use of oral contraceptives with longer duration (5 years or more) had an even stronger reduced risk of non-Hodgkin's lymphoma compared with shorter-duration use of oral contraceptives, and people who had used oral contraceptives before 1970 had an even greater reduced risk than did people had used oral contraceptives after 1970. It is known that earlier formulations contained a higher level of estrogen than more recent formulations. Our results are consistent with the findings reported by Nelson et al. (9). In our study, while oral contraceptive use was not associated with the risk of non-Hodgkin's lymphoma overall, there was a suggestion of reduced risk associated with longer duration of use and with uses started before 1970. Our recent investigation also showed a slightly reduced risk of non-Hodgkin's lymphoma associated with hormone replacement therapy (31).

It is interesting to note in our study that an increasing number of pregnancies and use of oral contraceptives were associated with a reduced risk of non-Hodgkin's lymphoma, while there was no clear risk relation with the estimated total months of ovulation. These results may indicate that exposure to very high levels of sex hormones may be needed to show a protective effect on non-Hodgkin's lymphoma risk. Our results also showed that early age at menarche was associated with a reduced risk of non-Hodgkin's lymphoma, while age at menopause was not associated with the risk. Early age at menarche and later age at menopause would result in a longer duration of ovulation and, thus, a longer duration of exposure to estrogens. This seemingly controversial result may also indicate that sex hormone exposures occurring early in life may be important for estrogens to have a protective effect against the development of non-Hodgkin's lymphoma.

The strengths and limitations involved in our study need to be considered in interpreting the results. One of the advantages is that, in this population-based case-control study, all incident cases were histologically confirmed by two experienced and independent pathologists. The histologic confirmation not only reduced the potential for disease misclassification but also allowed us to evaluate the relation by non-Hodgkin's lymphoma subtypes, which is necessary when considering the heterogeneity of the disease. Previous epidemiologic studies of reproductive factors and non-Hodgkin's lymphoma risk have failed to examine the relation by non-Hodgkin's lymphoma subtypes.

Menstrual and reproductive history was collected based on self-reporting by study participants. Previous studies have generally reported a high degree of reliability for reporting menstrual and reproductive history (32–36). Moreover, since so little is known about the relation between menstrual and reproductive history and the risk of non-Hodgkin's lymphoma, any misclassification by self-report of menstrual and reproductive history is likely to be nondifferential.

A potential limitation of the study is the relatively low response rate from potentially eligible subjects, particularly for older controls. However, it is unlikely that the refusal to participate in the study was related to their specific menstrual and reproductive history. In addition, given the several consistent associations observed in our studies with the majority of previous epidemiologic studies including age at first pregnancy, abortion, and miscarriage, selection bias resulting from the low participation rate is unlikely to play a critical role for the observed associations in this study. Finally, while the relatively large sample size allowed us to evaluate the overall relation between non-Hodgkin's lymphoma and menstrual and reproductive factors, the statistical power by non-Hodgkin's lymphoma subtype may still be limited. We could not look at specific subtypes separately for lack of power. The non-Hodgkin's lymphoma subtypes used in this study in fact represent relatively broad histologic subtype groupings of non-Hodgkin's lymphoma.

In summary, our study suggests a reduced risk of non-Hodgkin's lymphoma associated with increasing number of pregnancies and an increased risk of non-Hodgkin's lymphoma associated with late age at first menstrual period. The risk of non-Hodgkin's lymphoma associated with menstrual and reproductive factors appears to vary according to non-Hodgkin's lymphoma subtype. Future large population-based epidemiologic studies are needed to confirm the findings.

ACKNOWLEDGMENTS

The authors thank the Connecticut Tumor Registry of the Connecticut Department of Public Health for certain data used in this study. They also thank the institutions that allowed access to diagnostic materials and pathology reports, including the following hospitals: Bradley Memorial Hospital, Bridgeport Hospital, Bristol Hospital, Charlotte Hungerford Hospital, Danbury Hospital, Day-Kimball Hospital, Greenwich Hospital, Griffin Hospital, Hartford Hospital, Hospital of St. Raphael, Johnson Memorial Hospital, Lawrence and Memorial Hospital, Manchester Memorial Hospital, Middlesex Hospital, MidState Medical Center, Milford Hospital, New Britain General Hospital, New Milford Hospital, Norwalk Hospital, Rockville General Hospital, Sharon Hospital, Stamford Health System, St. Francis Hospital and Medical Center, St. Mary's Hospital, St. Vincent's Medical Center, Waterbury Hospital, William W. Backus Hospital, Windham Hospital, and Yale-New Haven Hospital.

The authors assume full responsibility for analyses and interpretation of these data.

REFERENCES

1. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends:

United States and international data. Cancer Res 1992; 52(suppl):5432s–40s.
2. Holford TR, Zheng T, Mayne ST, et al. Time trends of non-Hodgkin's lymphoma: are they real? What do they mean? Cancer Res 1992;52(suppl):5443s–6s.
3. Zheng T, Mayne ST, Boyle P, et al. Epidemiology of non-Hodgkin lymphoma in Connecticut. 1935–1988. Cancer 1992; 70:840–9.
4. Tavani A, Pregnolato A, La Vecchia C, et al. A case-control study of reproductive factors and risk of lymphomas and myelomas. Leuk Res 1997;21:885–8.
5. Adami HO, Tsaih S, Lambe M, et al. Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study. Int J Cancer 1997;70:155–8. Erratum in: Int J Cancer 1997;71:705.
6. Olsson H, Olsson ML, Ranstam J. Late age at first full-term pregnancy as a risk factor for women with malignant lymphoma. Neoplasma 1990;37:185–90.
7. Cerhan JR, Habermann TM, Vachon CM, et al. Menstrual and reproductive factors and risk of non-Hodgkin lymphoma: the Iowa Women's Health Study (United States). Cancer Causes Control 2002;13:131–6.
8. Miller AB, Barclay TH, Choi NW, et al. A study of cancer, parity and age at first pregnancy. J Chronic Dis 1980;33:595–605.
9. Nelson RA, Levine AM, Bernstein L. Reproductive factors and risk of intermediate- or high-grade B-cell non-Hodgkin's lymphoma in women. J Clin Oncol 2001;19:1381–7.
10. La Vecchia C, Negri E, Franceschi S, et al. Long-term impact of reproductive factors on cancer risk. Int J Cancer 1993;53: 215–19.
11. Frisch M, Wohlfahrt J, Westergaard T, et al. Induced abortion and the risk of non-Hodgkin's lymphoma. Int J Cancer 1997; 71:127–8.
12. Cunningham FG, Gant NF, Leveno KJ, et al. Williams obstetrics. 21st ed. New York, NY: McGraw-Hill, 2001.
13. Cheleuitte D, Mizuno S, Glowacki J. In vitro secretion of cytokines by human bone marrow: effects of age and estrogen status. J Clin Endocrinol Metab 1998;83:2043–51.
14. Jilka RL, Hangoc G, Girasole G, et al. Increased osteoclast development after estrogen loss: mediation by interleukin-6. Science 1992;257:88–91.
15. Girasole G, Jilka RL, Passeri G, et al. 17 Beta-estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts in vitro: a potential mechanism for the antiosteoporotic effect of estrogens. J Clin Invest 1992;89:883–91.
16. Saucedo R, Rico G, Basurto L, et al. Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response. Gynecol Obstet Invest 2002;53:114–17.
17. Rachon D, Mysliwska J, Suchecka-Rachon K, et al. Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women. J Endocrinol 2002;172:387–95.
18. Emilie D, Coumbaras J, Raphael M, et al. Interleukin-6 production in high-grade B lymphomas: correlation with the presence of malignant immunoblasts in acquired immunodeficiency syndrome and in human immunodeficiency virus-seronegative patients. Blood 1992;80:498–504.
19. Preti HA, Cabanillas F, Talpaz M, et al. Prognostic value of serum interleukin-6 in diffuse large-cell lymphoma. Ann Intern Med 1997;127:186–94.
20. Herrinton LJ. Epidemiology of the Revised European-American Lymphoma Classification subtypes. Epidemiol Rev 1998; 20:187–203.
21. Morton LM, Holford TR, Leaderer B, et al. Alcohol use and risk of non-Hodgkin's lymphoma among Connecticut women (United States). Cancer Causes Control 2003;14:687–94.
22. Percy C, Van Holten V, Muir C. International classification of diseases for oncology. 2nd ed. Geneva, Switzerland: World Health Organization, 1990.
23. Kristal AR, Feng Z, Coates RJ, et al. Associations of race/ethnicity, education, and dietary intervention with the validity and reliability of a food frequency questionnaire: the Women's Health Trial Feasibility Study in Minority Populations. Am J Epidemiol 1997;146:856–69. Erratum in: Am J Epidemiol 1998;148:820.
24. Casagrande JT, Louie EW, Pike MC, et al. "Incessant ovulation" and ovarian cancer. Lancet 1979;2:170–3.
25. Vorherr H. Contraception after abortion and post partum. An evaluation of risks and benefits of oral contraceptives with emphasis on the relation of female sex hormones to thromboembolism and genital and breast cancer. Am J Obstet Gynecol 1973;117:1002–25.
26. Kinlen LJ, Peto J, Doll R, et al. Cancer in patients treated with immunosuppressive drugs. (Letter). BMJ (Clin Res Ed) 1981; 282:474.
27. Hoover RN. Lymphoma risks in populations with altered immunity—a search for mechanism. Cancer Res 1992; 52(suppl):5477s–8s.
28. Luppi P. How immune mechanisms are affected by pregnancy. Vaccine 2003;21:3352–7.
29. Schiff D, Suman VJ, Yang P, et al. Risk factors for primary central nervous system lymphoma: a case-control study. Cancer 1998;82:975–82.
30. Beiderbeck AB, Holly EA, Sturkenboom MC, et al. No increased risk of non-Hodgkin's lymphoma with steroids, estrogens and psychotropics (Netherlands). Cancer Causes Control 2003;14:639–44.
31. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–28.
32. Bean JA, Leeper JD, Wallace RB, et al. Variations in the reporting of menstrual histories. Am J Epidemiol 1979;109:181–5.
33. Rohan TE, Record SJ, Cook MG. Repeatability of interview-derived socio-demographic and medical information. J Clin Epidemiol 1988;41:763–70.
34. Kelly JP, Rosenberg L, Kaufman DW, et al. Reliability of personal interview data in a hospital-based case-control study. Am J Epidemiol 1990;131:79–90.
35. Cumming RG, Klineberg RJ. A study of the reproducibility of long-term recall in the elderly. Epidemiology 1994;5:116–19.
36. Bosetti C, Tavani A, Negri E, et al. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001;54:902–6.